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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/845,717	05/02/2001	Soren Nielsen	NIELSEN=3B	3818

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BROWDY AND NEIMARK, P.L.L.C.
624 Ninth Street, N.W.
Washington, DC 20001

EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/845,717	NIELSEN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7,12-18,20 and 23-43* is/are pending in the application.

4a) Of the above claim(s) *3,4,6,7,12-18 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,20,23,26-32,34 and 36-43* is/are rejected.

7)☒ Claim(s) *25,33 and 35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment filed 20 September 2004 has been entered in full. New claims 25-43 were entered. Claims 8-10 and 19 were cancelled. Claims 1, 2, 5, 20, 23, 25-43 are under examination.

The information disclosure statement (IDS) filed 20 September 2004 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Matter of Record

Applicant requested clarification of the status of the instant application and the restriction. The Examiner told Applicant that the previous Office Action (19 March 2004) was made Non-Final. The Examiner told Applicant that the re-restriction (11 August 2004), mailed in error, was intended for co-pending application 09/845,716.

Withdrawn Objections And/Or Rejections

The rejection to claims 1, 2, 5, 8-10, 19, 20, 22 and 23 under 35 U.S.C. 112, first paragraph, written description, as set forth at pages 8-10 of the previous Office Action (19 March 2004) is *withdrawn* in view of the amendment (20 September 2004).

The rejection to claims 1, 19, 22 and 23 under 35 U.S.C. 102(b) as being anticipated by Delgado Hernandez *et al.,* Neuroimmunomodulation 6:187-192, 1999, as set forth at pages 10-11 of the previous Office Action (19 March 2004) is *withdrawn* in view of the amendment (20 September 2004).

The rejection to claims 1 and 9 under 35 U.S.C. 102(b) as being anticipated by Akamatsu *et al.,* US Patent No. 4,745,099, as set forth at page 11 of the previous Office Action (19 March 2004) is *withdrawn* in view of the amendment (20 September 2004).

The rejection to claims 1, 5, 9, 10 under 35 U.S.C. 103(a) as being unpatentable over Delgado Hernandez *et al.,* Neuroimmunomodulation 6:187-192, 1999 in view of Akamatsu *et al.,* US Patent No. 4,745,099, as set forth at pages 11-13 of the previous Office Action (19 March 2004) is *withdrawn* in view of the amendment (20 September 2004).

Claim Rejections - 35 USC § 112 First Paragraph, Enablement

Claims 1 and 20 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The basis for this rejection is set forth at pages 5-8 of the previous Office Action (15 June 2001, Paper No. 13).

Applicant argues that the model of acute lung inflammation induced by LPS inhalation is widely used as a model for COPD, as evidenced by more than 100 published papers using the model. Applicant states that experimentally LPS inhalation induces an inflammatory response with neutrophil and eosinophil infiltrations that mimics the inflammatory response seen during an exacerbation in COPD. Applicant

cites submitted reference Saetta *et al.* Am. J. Respir. Crit. Care Med. 150:1646-1642, 1994.

Applicant's arguments have been fully considered but not deemed persuasive. As was stated in the previous Office Action, Shapiro (American Journal of Respiratory Cell and Molecular Biology, 2000) teaches that a variety of chemicals and irritants have been used in experimental animals to induce inflammation and emphysema, including LPS. Shapiro states that all have contributed to the knowledge of lung injury, but none have replicated exposure to cigarette smoke as a model for authentic COPD (page 4, 4th paragraph). Saetta *et al.* (Am. J. Respir. Crit. Care Med. 150:1646-1642, 1994) does not teach the model of acute lung inflammation induced by LPS inhalation as a model of COPD. It is suggested that Applicant cite the page number where such is taught by Saetta *et al.*

The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

Claim Rejections - 35 USC § 112 First Paragraph, Scope of Enablement

Claims 1, 30, 31, 32, 34, 37, 38, 42, 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

the method of claim 1, further comprising administration of an anti-inflammatory amount of an alpha-MSH equivalent which **is a peptide comprising the sequence His-Phe-Arg-Trp OR Lys-Pro-Val,** wherein said peptide binds to an alpha-MSH receptor and/or an melanocortin receptor, and thereby exercises anti-inflammatory activity

does not reasonably provide enablement for:

an alpha-MSH equivalent which is **a peptide comprising the sequence of "any four amino acid" or "any three amino acid fragment" of alpha-MSH.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant states that studies have shown that it is possible to make substitutions of Phe within this 4 amino acid structure with either D-Phe or D-Nal and still have marked affinity against the MC1 receptor. Applicant cites Wikenberg *et al.*

Applicant's arguments have been fully considered but not deemed persuasive because the arguments do not address the issue regarding the functioning sequences of alpha-MSH. The reference submitted by Applicant (Wikberg *et al.*, Pharm Research 42:393-420, 2000) teaches that alpha-MSH contain two centres of activity for induction of melanin dispersion in amphibian skin assays, His-Phe-Arg-Trp and Lys-Pro-Val. The His-Phe-Arg-Trp region in alpha-MSH is suggested to represent the core for the binding of melanocortic peptides to the MC receptors. Wikberg *et al.* teach that MSH 11-13 (Lys-Pro-Val) had anti-inflammatory activity as it reduced ear swelling in mice and can mimic many of the actions of alpha-MSH (pages 405-407). Thus, Wikberg *et al.* teach activity with *specific alpha-MSH peptide sequences*.

The instant claims are drawn to peptides comprising the sequence of any four or three amino acid fragment of alpha-MSH. It is in no way predictable that randomly selected fragments of alpha-MSH would afford a protein having activity (anti-

inflammatory activity) comparable to the one disclosed. Szardenings *et al.* (reference submitted by Applicant, WO 99/57148) teach that peptide MSO5 (Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH2) and MSO9 (Ser-Ser-Ile-Ile-Ser-His-dPhe-Arg-Trp-Gly-Lys-Pro-Val-NH2) share the capacity of alpha-MSH to inhibit inflammation. Dooley *et al.* (reference submitted by Applicant, WO 99/21571) teach that MC receptor peptide ligand HP 467 (Ac-Nle-Gln-His-(p(I)-D-Phe)-Arg-(D-Trp)-Gly-NH2) decreases tumor necrosis factor levels in LPS treated mice. The references submitted by Applicant demonstrate that **specific amino acids in the alpha-MSH sequence** are critical to the protein's structure/function relationship and binding to the MC receptor.

The instant specification teaches that inflammation of the lungs (asthma) was induced by LPS inhalation (page 26, lines 5-10). LPS inhalation induces a dramatic influx of inflammatory cells in the lung tissue (page 33, lines 25-33). The specification teaches that alpha-MSH, epoitin or the combination of alpha-MSH and epoitin reduced the influx of inflammatory cell in the lung exposed with LPS (page 33, line 35-page 34, line 20). The instant specification fails to teach that a peptide comprising the sequence of any four amino acid or three amino acid fragment of alpha-MSH will reduce the influx of inflammatory cells in the lung exposed to LPS. Without sufficient guidance, the changes which can be made in the structure and still maintain sufficient activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

Due to the large quantity of experimentation necessary to generate the derivatives recited in the claims and screen same for anti-inflammatory activity, the lack

of direction/guidance presented in the specification regarding which structural features are required in order to provide anti-inflammatory activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes that specific positions in the alpha-MSH sequence are critical to the protein's structure/function relationship and binding to the MC receptor and the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112 First Paragraph, Written Description, New Matter

Claims 1 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed: "is administered in a plurality of separate dosings" (claim 5). Applicant's amendment, filed 20 September 2004, asserts that no new matter has been added, but does not provide sufficient direction for the written description for the above-mentioned "limitations".

The specification as filed does not provide a written description or set forth the metes and bounds of this "limitations". The instant claims now recite limitations which

were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide specific sufficient written support for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections - 35 USC § 112 Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 37-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 37-43 are indefinite. The instant claims recite that the peptide comprises the sequence Lys-Pro-Val, however the peptide actually consist of a sequence which does not recite Lys-Pro-Val. For example, claim 37 is drawn to a peptide comprising the sequence Lys-Pro-Val, wherein said peptide *consists of the sequence*

A1-B2-C3-D4, wherein: A1 is αFmLys or His;

B2 is Arg, D-Thr or pCl-f,

C3 is Arg, L-Cha or D-Ile, and

D4 is D-Nal or D-Arg.

The instant peptide no longer comprises the sequence Lys-Pro-Val.

Claim 38 is indefinite because it recites the limitation "which substance binds". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102(b)

Claims 1, 2, 23 and 39 are rejected under 35 U.S.C. 102(b) as being anticipated by Akamatsu *et al.*, US Patent No. 4,745,099 (cited in previous Office Action).

The instant claims are drawn to a method for treatment or prophylaxis of a non-ischemic condition characterized by inflammation of the lung or airways, the method comprising administering a therapeutically or prophylactically effective amount of an erythropoietin (EPO) to the individual in need thereof.

Akamatsu *et al.* teach the administration of human EPO for treatment of the anemia of malignant tumors (non-ischemic condition) (abstract, claims). Akamatsu *et al.* teach the administration of EPO in Lewis lung carcinoma mouse models (column 6, lines 29-52 and Figures 1 and 2). Akamatsu *et al.* teach the alleviation of anemia in the carcinoma mouse models upon administration of erythropoietin (column 6, lines 29-52 and Figures 1 and 2). Lewis lung carcinoma mouse models would exhibit inflammation of the lung or airways. Lung cancer can be caused by smoking (chemical trauma).

Claim Rejections - 35 USC § 103(a)

Claims 1, 26, 27, 28, 29, 30, 31, 36, 40-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Akamatsu *et al.*, US Patent No. 4,745,099 in view of

Delgado Hernandez *et al.*, Neuroimmunomodulation 6:187-192, 1999 (cited in the previous Office Action).

The instant claims are drawn to a method for treatment or prophylaxis of a non-ischemic condition characterized by inflammation of the lung or airways, the method comprising administering a therapeutically or prophylactically effective amount of an erythropoietin (EPO) to the individual in need thereof, further comprising administration of an anti-inflammatory amount of alpha-MSH. The teachings of Akamatsu *et al.* are described above. Akamatsu *et al.* do not teach the administration of alpha-MSH for a non-ischemic condition characterized by inflammation of the lung or airways.

Delgado Hernandez *et al.* teach that administration of endotoxin to mice, which induced endotoxemia (non-ischemic condition characterized by inflammation of the lung or airways) and increased circulating TNF alpha and nitric oxide. Delgado Hernandez *et al.* teach that central administration of alpha-MSH significantly modulated TNF alpha and NO increases in lung and liver. Delgado Hernandez *et al.* also teach that lung myeloperoxidase, a marker of neutrophil infiltration was enhanced by LPS injection (induced a non-ischemic condition characterized by inflammation of the lung or airways) and was reduced by administration of alpha-MSH (page 189, results and page 191, 1st and 4th paragraph). Delgado Hernandez *et al.* teach the anti-inflammatory activity of alpha-MSH.

The alpha-MSH protein employed by Delgado Hernandez *et al.* is full length, and thus comprises the sequences Lys-Pro-Val; Gly-Lys-Pro-Val; His-Phe-Arg (applies to claims 28-30, 41 and 42). Instant claims 31, 36 and 43 recite "a peptide comprising at

least a four amino acid fragment of alpha-MSH" "a peptide fragment, at least three amino acids long, of alpha-MSH and comprises the sequence Lys-Pro-Val" and "a peptide comprising at least a four amino acid fragment of alpha-MSH", respectively. The instant claims are included in the rejection because of the recitation "at least", which is the minimum length. Furthermore, the instant claims do not specify the length of the fragment.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Akamatsu *et al.* and Delgado Hernandez *et al.* to make the instant invention of a method for treatment or prophylaxis of a non-ischemic condition characterized by inflammation of the lung or airways, the method comprising administering a therapeutically or prophylactically effective amount of an erythropoietin (EPO) to the individual in need thereof, further comprising administration of an anti-inflammatory amount of alpha-MSH. The motivation and expected success is provided by both inventors who demonstrate efficacy upon the administration of alpha-MSH or EPO.

Because both inventors teach the efficacy of treatment of non-ischemic condition characterized by inflammation of the lung or airways upon administration of alpha-MSH or EPO, it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose (i.e. treating non-ischemic condition characterized by inflammation of the lung or airways), in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re

Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980) (citations omitted) (Claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious). See also In re Crockett, 279 F.2d 274, 126 USPQ 186 (CCPA 1960) (Claims directed to a method and material for treating cast iron using a mixture comprising calcium carbide and magnesium oxide were held unpatentable over prior art disclosures that the aforementioned components individually promote the formation of a nodular structure in cast iron.); and Ex parte Quadranti, 25 USPQ2d 1071 (Bd. Pat. App. & Inter. 1992) (mixture of two known herbicides held prima facie obvious).

Claim Objections

Claims 25, 33 and 35 are objected to because they depend from a rejected claim.

Claim 38 is objected to because it's drawn to an improper Markush group (see line 14).

Sequence Rules

The specification is not in compliance with 37 CFR 1.821-1.825 of the Sequence Rules and Regulations. When the description of a patent application discusses a sequence listing that is set forth in the "Sequence Listing" in accordance with paragraph (c) of the Sequence Rules and Regulations, reference must be made to the sequence by use of the assigned identifier (SEQ ID NO:), in the text and claims of the patent application.

37 CFR 1.821(a) presents a definition for nucleotide and/or amino acid sequences. This definition sets forth limits in terms of numbers of amino acids and/or numbers of nucleotides, at or above which compliance with the sequence rules is required. Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Please see MPEP section 2422.01.

The specification refers to sequences in claims 32, 33 and 38 but does not identify the sequences by their sequence identifiers.

Applicant states that the sequence rules do not require listing of peptides containing D-amino acids or sequences with fewer than four specifically defined amino acids. Applicant cites MPEP 2422.01, which states that the presence of one or more D-amino acids in a sequence will exclude that sequence from the scope of the rules. However, claims 32, 33 and 38 recite four amino acids and encompasses L- **OR** D-amino acids.

Appropriate correction is required. Applicant must submit a response to this Office Action and compliance with the sequence rules within the statutory period set for response to this Office Action.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
12/2/04

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER